



OLEM Perspective on Non-Targeted Analysis for Emergency Response

Christina Langlois-Miller

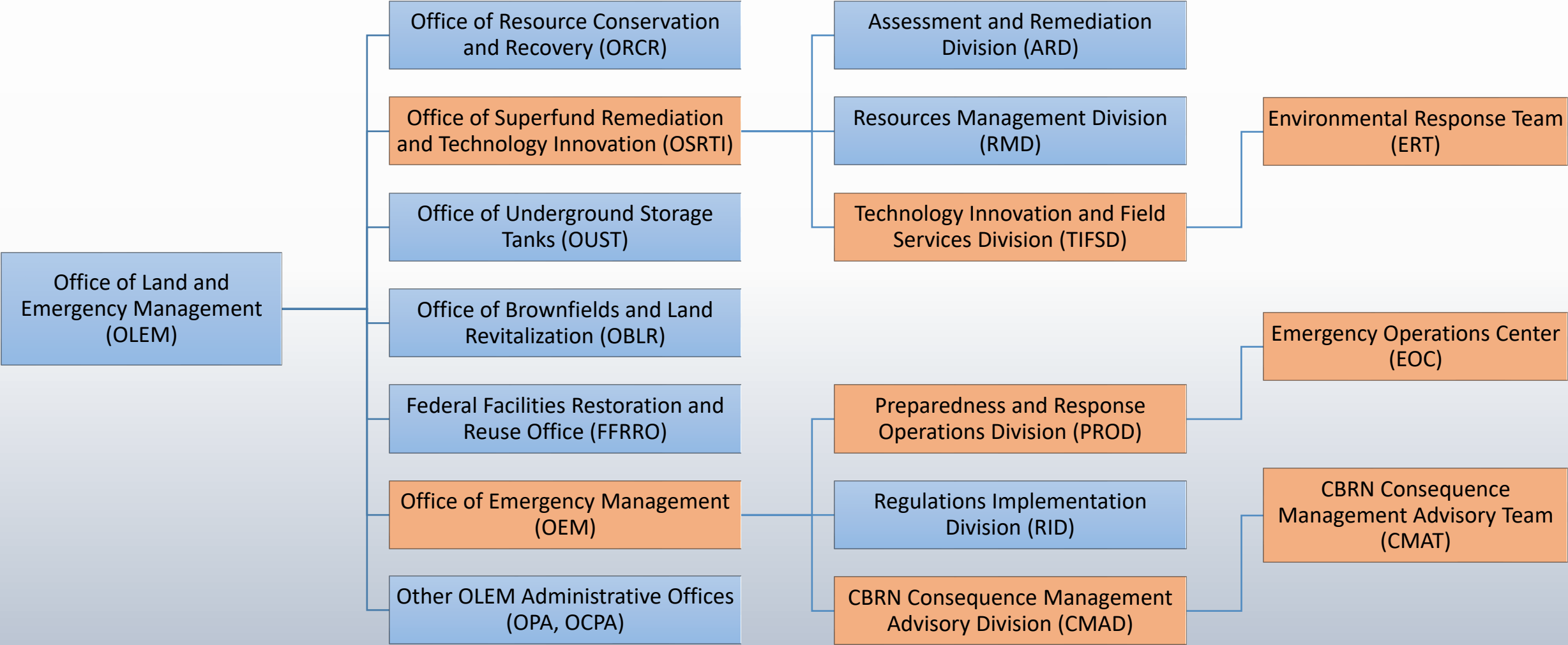
CBRN Consequence Management Advisory Division

Office of Emergency Management

The views expressed in this presentation are those of the author(s) and do not necessarily represent the views or the policies of the U.S. Environmental Protection Agency (USEPA)



OLEM Organization





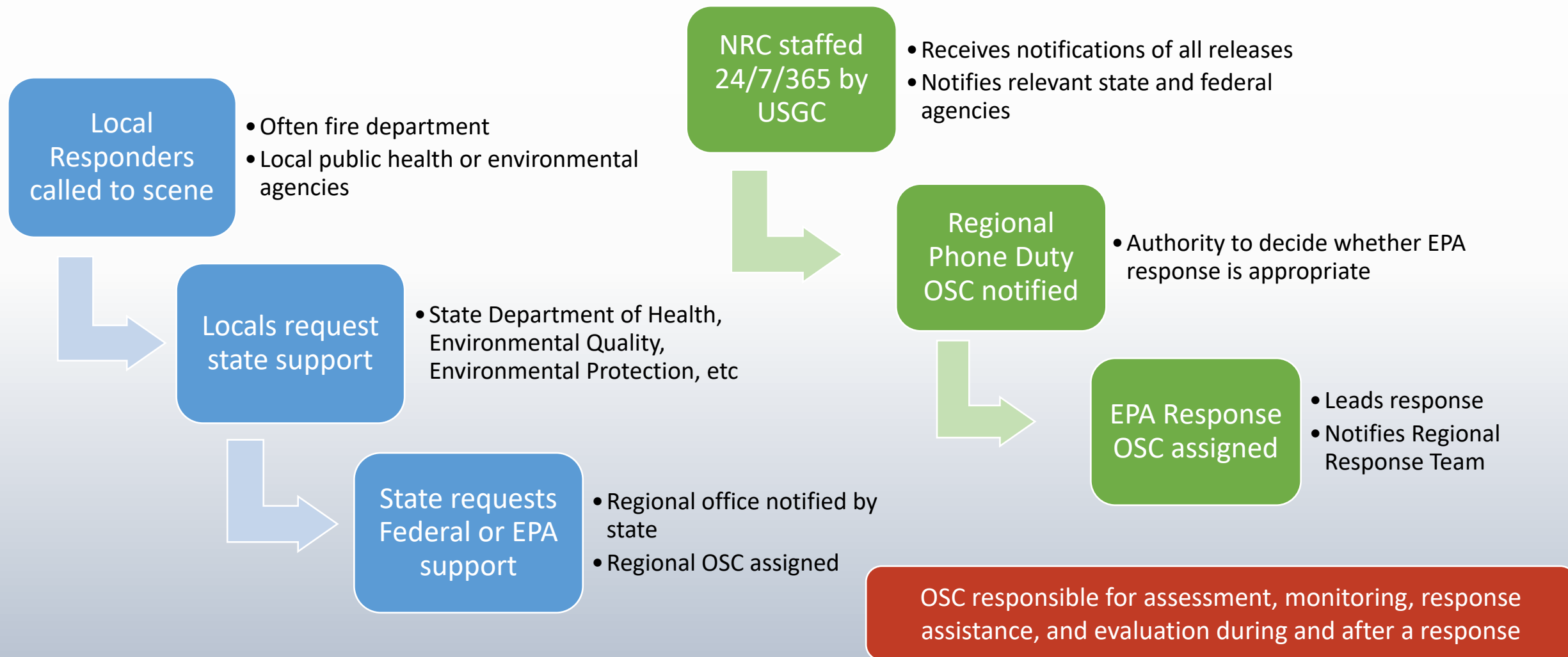
EPA's Emergency Response Authorities and Responsibilities



- EPA National Oil and Hazardous Substances National Contingency Plan (NCP)
 - Framework for responding to oil spills and hazardous substance releases
 - Covers emergency response authority under various EPA statutes
 - Oil Pollution Act (OPA)
 - Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)
 - Clean Water Act (CWA)
- FEMA National Response Framework
 - Scalable, flexible, and adaptable guide for how the nation responds to disasters and emergencies
 - Uses National Incident Management System – key roles and responsibilities
 - Emergency Support Functions describe federal coordinating structures
 - ESF #10 – Oil and Hazardous Materials Response
 - EPA is ESF #10 Coordinator, primary agencies are EPA, DHS, USCG
 - Activated for Stafford Act response, at discretion of Secretary of Homeland Security, or in response to request for Federal support
 - EPA deployment contingent on Mission Assignment – specifies tasks and funding



Paths to EPA Involvement





Resources for OSCs – EPA Special Teams



CBRN Consequence Management Advisory Team (CMAT)

- CBRN experts
- Mobile labs for confirmatory analysis of chemical warfare agents and toxic industrial compounds (TICs) - PHILIS
- Aerial detection system for TICs and oil spills - ASPECT
- Laboratory network for surge capacity - ERLN

Environmental Response Team (ERT)

- Oil and hazmat response experts
- Air monitoring team
- Mobile trace atmospheric gas analyzers - TAGA
- Fate and transport modeling

Radiological Emergency Response Team (RERT)

- Radiation risk monitoring
- Cleanup of radioactive substances

National Criminal Enforcement Response Team (NCERT)

- Forensic evidence collection
- Law enforcement liaisons
- Protective escorts for responders



Potential Applications of NTA in OLEM Emergency Response Capabilities



- Non-targeted analysis (NTA) could be used to rapidly narrow down composition of unknown spills or intentional releases of unknown chemicals
 - Specific chemical composition is important for:
 - Determination of EPA authority – must be a listed hazardous waste, substance, etc under some EPA authority for responsible party financial liability
 - Selection of decontamination techniques and establishing clearance goals
- NTA may be able to be used to identify degradation products and/or complex mixtures of hazardous chemicals
 - Potentially useful for long-term monitoring in addition to emergency response
 - Potentially useful for determining the source of contamination using chemical profile matching
 - Potential applications for identification of chemical warfare agents (traditional and fourth generation) – limited laboratory capacity
 - Potential applications for identification of pharmaceutical based agents (fentanyl and analogs) – many potential agents

The Use of Non-Targeted Analysis for Rapid and Emergency Response

Seth Newton, Christina Langlois-Miller, Allison Phillips,
John Sloop, Antony Williams, Jennifer Gundersen, Jon
Sobus, Elin Ulrich, Alex Chao

Office of Research and Development

Office of Emergency Management

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Why NTA in Rapid Response?

- In 2019, ~26,000 logged environmental discharges → 37% of unknown composition
 - “unknown oil”, “unknown toxic chemicals”, “unknown green liquid”
- EPA relies on a brick-and-mortar lab network called the Emergency Response Lab Network (ERLN) and Portable High-Throughput Integrated Laboratory Identification Systems (PHILIS)
- ERLN and PHILIS utilize mostly targeted analytical chemistry methods, although some non-targeted work is done

PHILIS laboratories are staged at two strategic locations within the United States to facilitate a 24-hour response window.




CASTLE
ROCK, CO

ERLN laboratories (n= ~140 ●), regional mobile laboratories (🚚), and Trace Atmospheric Gas Analyzer units (🚌) are dispersed across the United States and can be activated to perform additional analyses.

Phillips et al., ET&C 2021.

Environmental Toxicology and Chemistry

critical perspectives |  Full Access

A Framework for Utilizing High Resolution Mass Spectrometry and Non-Targeted Analysis (NTA) in Rapid Response and Emergency Situations

Allison L. Phillips, Antony J. Williams, Jon R. Sobus, Elin M. Ulrich, Jennifer Gundersen, Christina Langlois-Miller, Seth R. Newton 

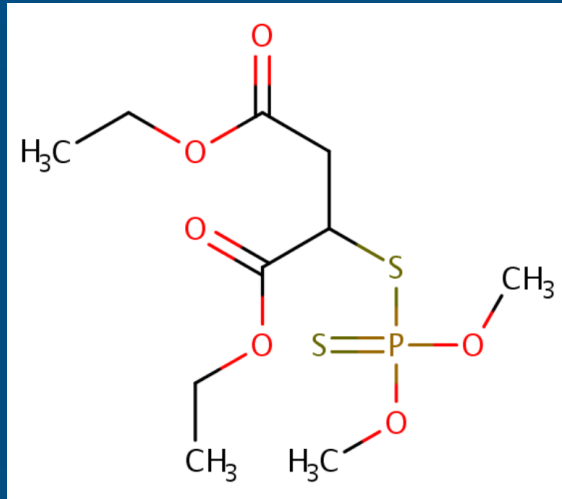
First published: 20 August 2021 | <https://doi.org/10.1002/etc.5196>

(Submitted 28 June 2021; Returned for Revision 26 July 2021; Accepted 17 August 2021)

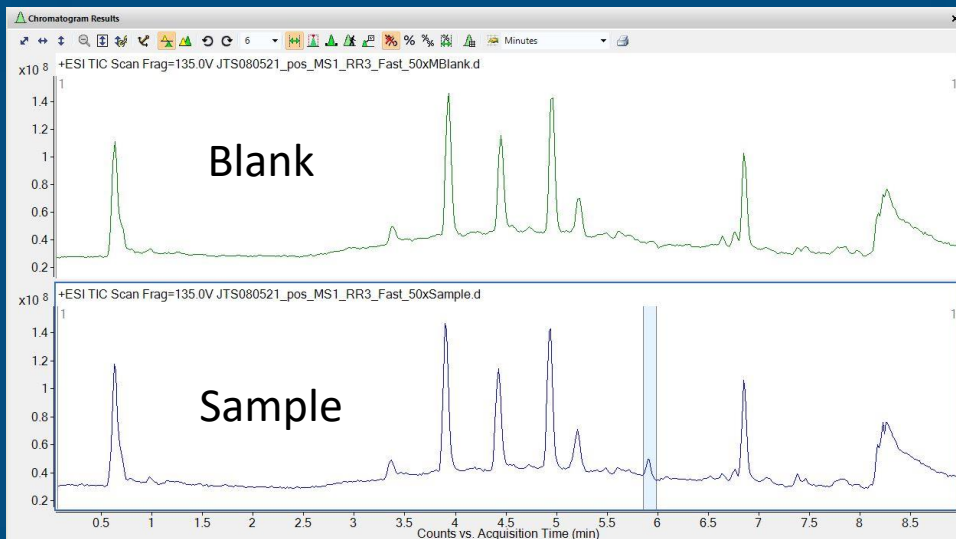
This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/etc.5196

Mock Scenario 1: A Chemical Warfare Agent in Alcohol

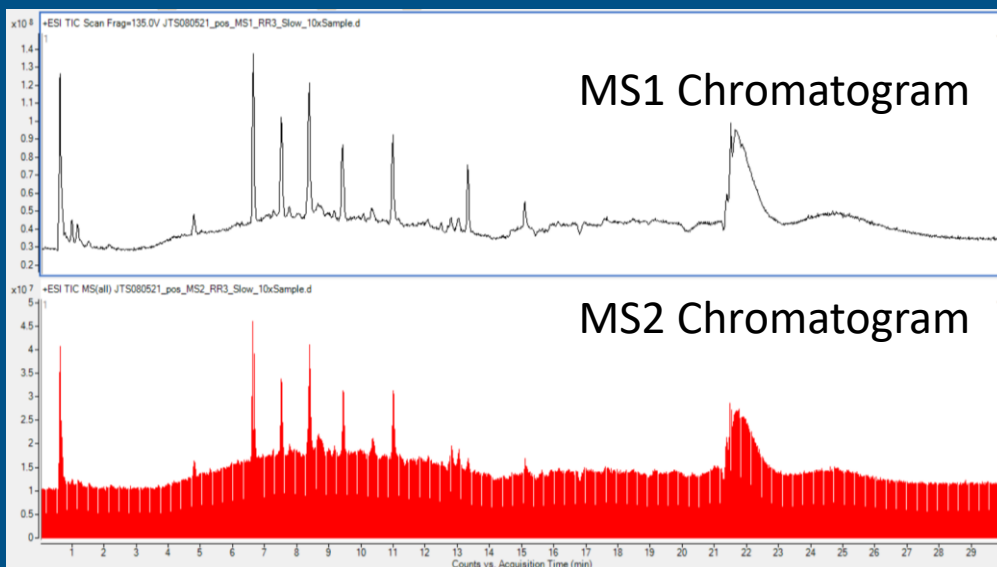
Malathion



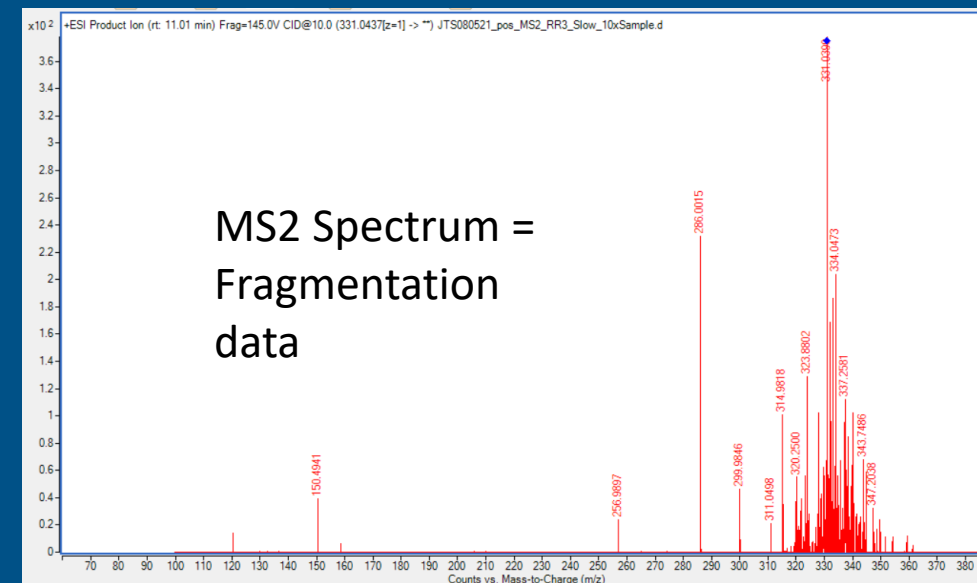
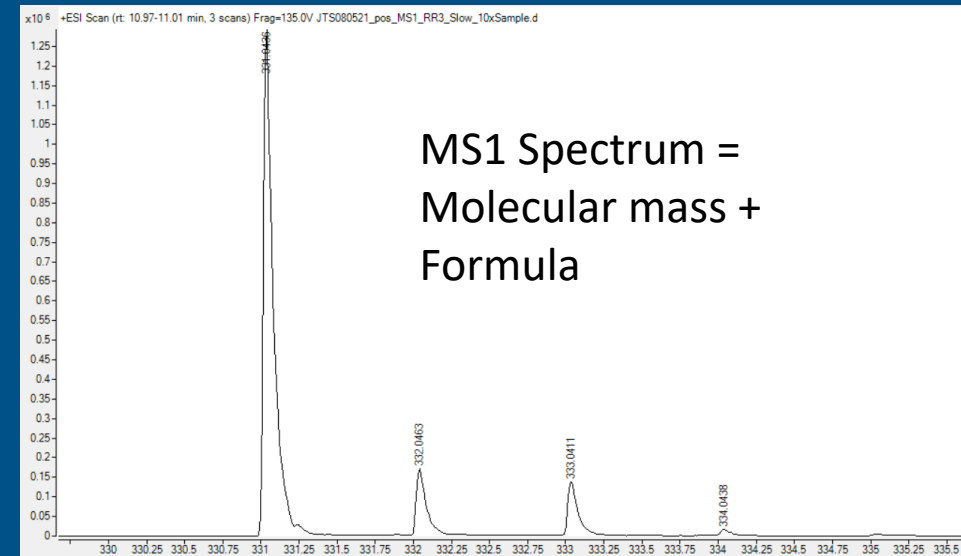
- Malathion is structurally similar to Novichok nerve agents, used in an attack in the UK in 2018
- One analyst spiked malathion into pure ethanol
- Another analyst was blind to the identity of the compound



Rapid Range Finding



Long Method



NTA: non-targeted analysis of MS data (beta)

[Contact Us](#)

Tools

MS1 Tool

Run MS1 Tool

MS1 Tool Algorithms

MS1 Tool QA/QC

MS1 Tool References

MS2 CFMID Tool

Documentation

Source Code

Run NTA MS1 Tool

Input	Value
Project name:	<input type="text" value="Example nta"/>
Positive MPP file (csv):	<input type="button" value="Choose File"/> No file chosen
Negative MPP file (csv):	<input type="button" value="Choose File"/> No file chosen
Adduct mass accuracy units:	<input type="text" value="ppm"/>
Adduct mass accuracy:	<input type="text" value="10"/>
Adduct retention time accuracy (mins):	<input type="text" value="0.05"/>
Tracer file (csv; optional):	<input type="button" value="Choose File"/> No file chosen
Tracer mass accuracy units:	<input type="text" value="ppm"/>
Tracer mass accuracy:	<input type="text" value="5"/>
Tracer retention time accuracy (mins):	<input type="text" value="0.1"/>
Min sample:blank cutoff:	<input type="text" value="3"/>
Min replicate hits:	<input type="range" value="2"/>
Max replicate CV:	<input type="text" value="0.8"/>
Parent ion mass accuracy (ppm):	<input type="range" value="5"/>
Discard features below this retention time (mins):	<input type="text" value="0.0"/>
Search dashboard by:	<input type="text" value="mass"/>
Save top result only?	<input type="text" value="no"/>
DSSTox search batch size (debugging):	<input type="text" value="150"/>

Defaults

Clear

Save Metadata?

Submit

NTA: non-targeted analysis of MS data (beta)

[Contact Us](#)

Tools

MS1 Tool

Run MS1 Tool

MS1 Tool Algorithms

MS1 Tool QA/QC

MS1 Tool References

MS2 CFMID Tool

Documentation

Source Code

NTA Output

Job ID: XIN4V113

Download results:

Final results

All files



Parameters for NTA

clean-
search

WebApp Output:

- QA/QC results of internal standards
- Cleaned, annotated file with chemicals

<https://qed.edap-cluster.com/nta/>

NTA WebApp: MS2 Spectra Fragmentation Prediction

NTA: non-targeted analysis of MS data (beta) [Contact Us](#)

Tools

- MS1 Tool
- MS2 CFMID Tool

Documentation

- Source Code

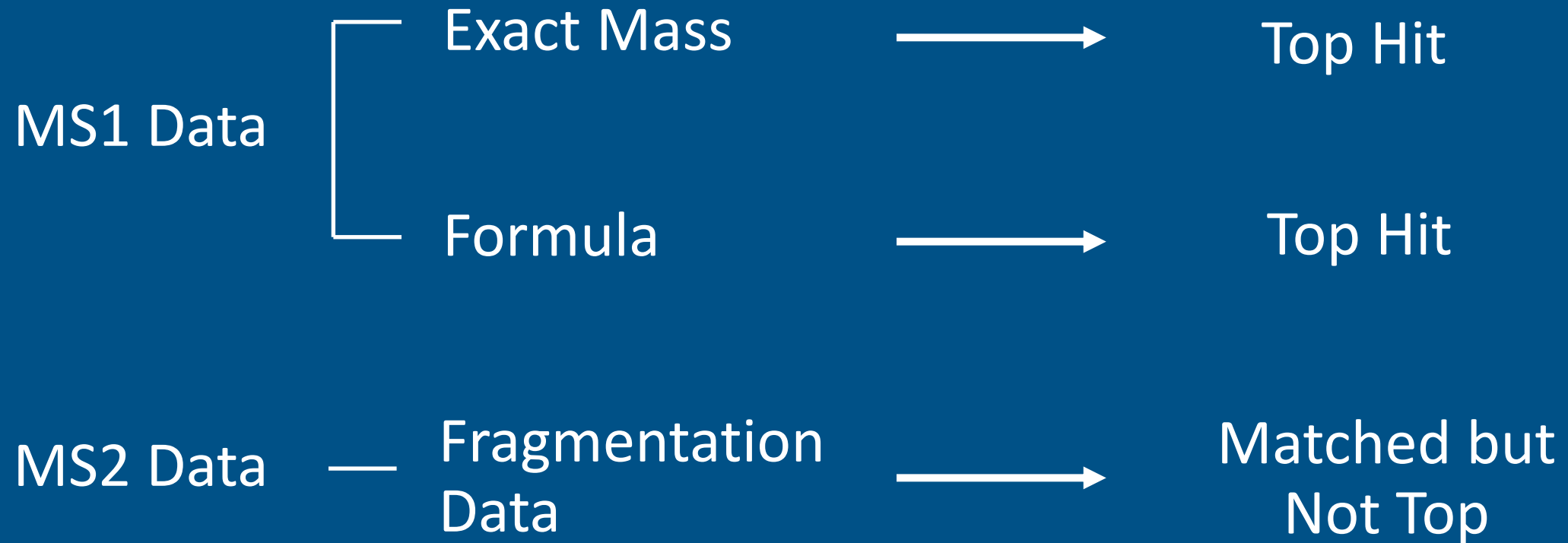
Run MS2 CFMID Tool

Input	Value
Project name:	<input type="text" value="Example ms2 nta"/>
Positive mode MS2 files (mgf):	<input type="button" value="Choose Files"/> No file chosen
Negative mode MS2 files (mgf):	<input type="button" value="Choose Files"/> No file chosen
Precursor mass accuracy (ppm):	<input type="text" value="10"/>
Fragment mass accuracy (Da):	<input type="text" value="0.02"/>



Spectra predicted using the Competitive Fragmentation Modeling for Metabolite Identification (CFM-ID) algorithm

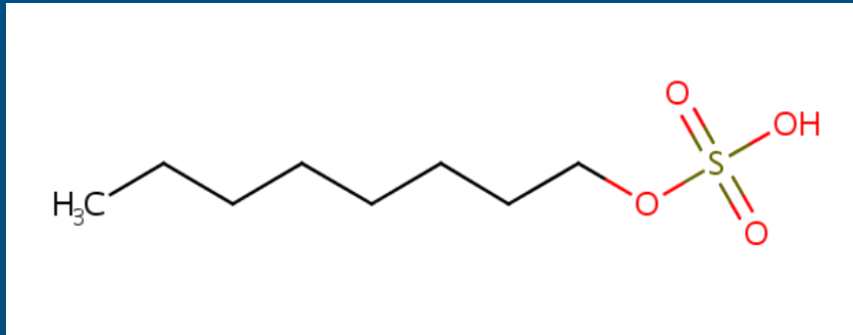
Mock Scenario 1: Identifying Malathion



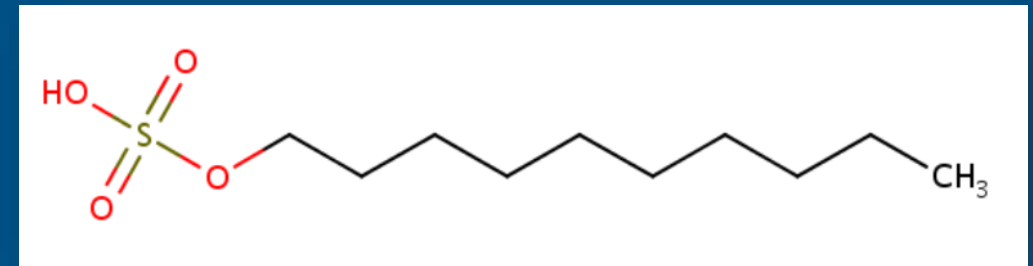
Analyst reported correct identification in 13 hours

Mock Scenario 2 – Aqueous Firefighting Foam (AFFF) Spilled into Surface Water

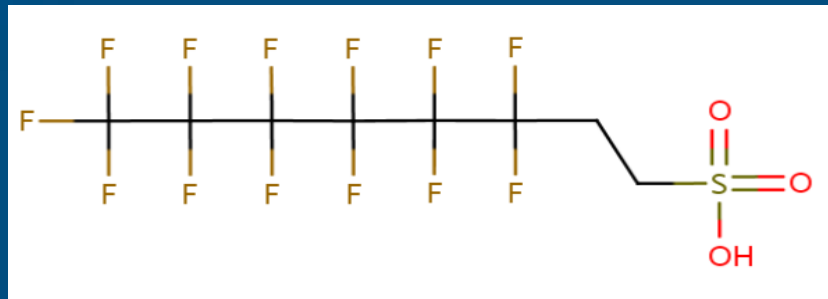
- Confident structure identification



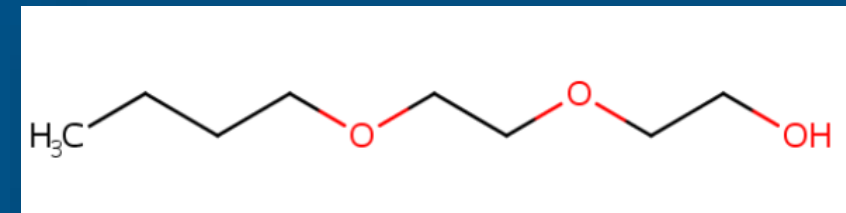
Octyl Hydrogen Sulfate



Decyl Hydrogen Sulfate

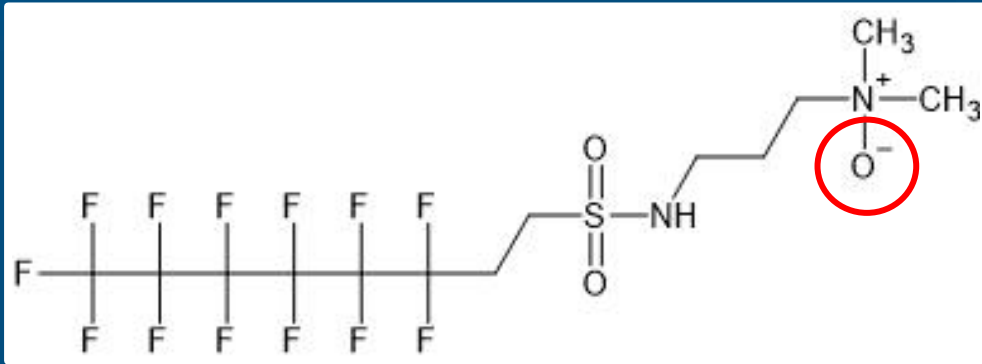


6:2 Fluorotelomer Sulfonic Acid

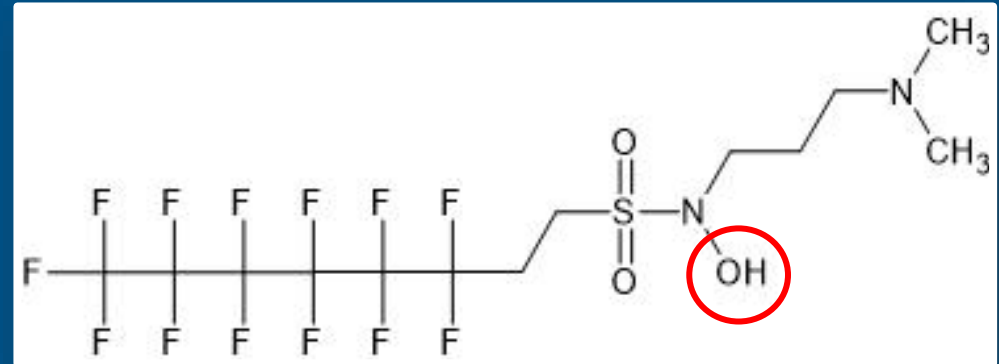


2-(2-Butoxyethoxy)ethanol

Mock Scenario 2 – Two Candidates



**N,N-Dimethyl-3-
((perfluorohexyl)ethylsulfonyl)
aminopropanamine N-oxide**



**N-[3-(Dimethylamino)propyl]-
3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluoro-N-
hydroxyoctane-1-sulfonamide**

Hazard Comparison Dashboard

Toxicity: VH - Very High H - High M - Medium L - Low I - Inconclusive N/A - Not Applicable Authority: Authoritative Screening QSAR Model

<input type="checkbox"/> Skipped (0) <input type="checkbox"/> Unlikely (0) <input type="checkbox"/> Filters (0) <input checked="" type="checkbox"/> Sorting (0) <input type="checkbox"/> Structure CAS Name	Human Health Effects									Ecotoxicity
	Acute Mammalian Toxicity			Genotoxicity Mutagenicity	Neurotoxicity	Systemic Toxicity	Skin Sensitization	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity
	Oral	Inhalation	Dermal		Single Exposure	Single Exposure				
110-11-2 Octyl hydrogen sul...	M			VH				H		M
142-98-3 Decyl hydrogen su...	M			H				H		H
80475-32-7 N,N-Dimethyl-3-(p...	I			I						I
27619-97-2 6:2 Fluorotelomer ...	M			VH						H
7399-66-8 NSC54390	I			H						M
112-34-5 2-(2-Butoxyethoxy...	M	I	L	L			I	M	H	L
958822-85-0 N-[3-(Dimethylami...	I			I						I

Summary of Conclusions

- NTA workflows have been adapted to cut down on response time
- Work best when the chemical(s) of interest is at higher concentrations than the background
- NTA workflows can be applied to complex mixtures, but response times may increase

Future Work

- More scenarios in complex matrices
- Adapt methods to GC
- Get a chance to apply this to a real-world scenario

Contributing Researchers



Credit: the Research Triangle Foundation

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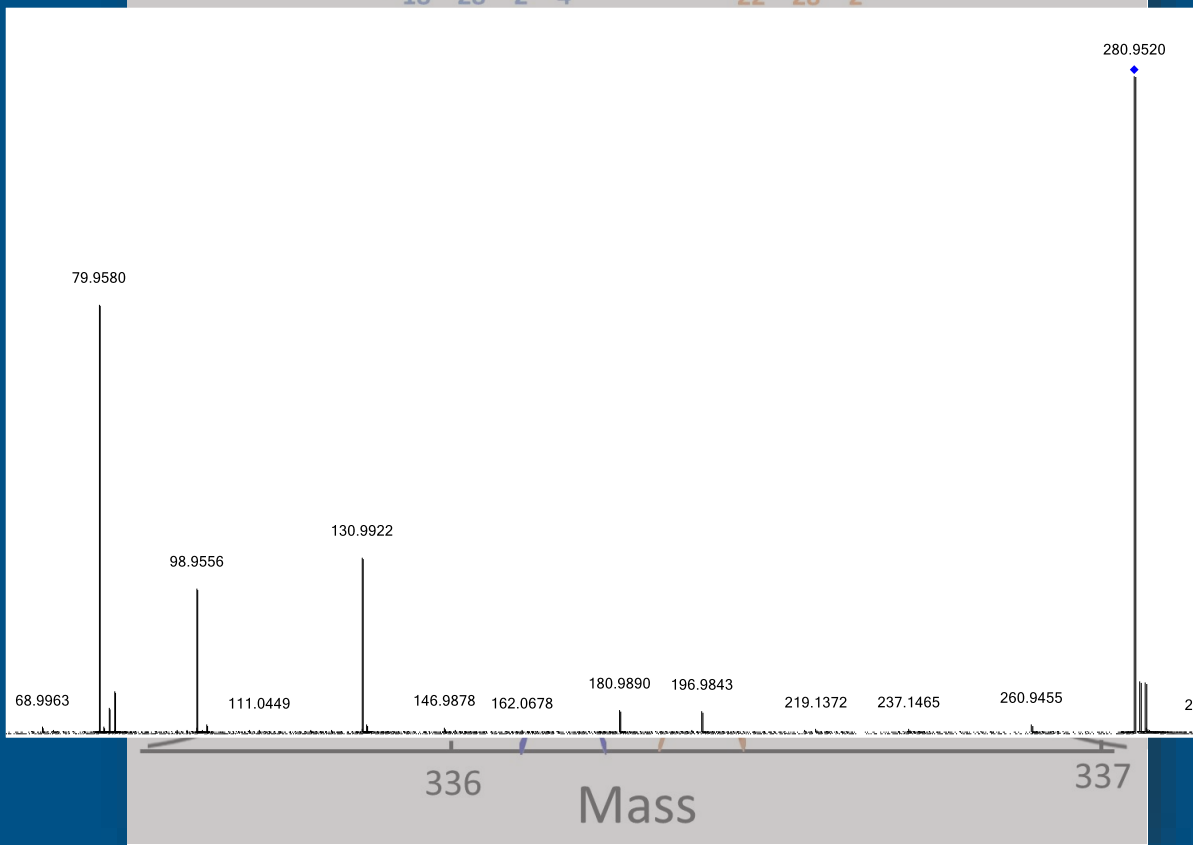
NTA and High Resolution Mass Spectrometry (MS)

Acebutolol

$C_{18}H_{28}N_2O_4$

Fentanyl

$C_{22}H_{28}N_2O$




MS1:

- Accurate mass of molecular ion
- Molecular formula prediction or matching


MS2:

- Fragmentation data used to match to spectral libraries (experimental or predicted)
- NTA utilizes both MS1 and MS2 data from HRMS, combined with informatics tools, for identification of unknown chemicals
- NTA is typically very slow and time-consuming

The Comptox Chemicals Dashboard

 United States Environmental Protection Agency

HomeAdvanced SearchBatch SearchLists ▼PredictionsDownloads



CompTox Chemicals Dashboard








883 Thousand Chemicals


ChemicalsProduct/Use CategoriesAssay/Gene

☐ Identifier substring search

See what people are saying, read the dashboard [comments!](#)
Cite the Dashboard Publication [click here](#)

Metadata

- ☐ Curation Level Details 
- ☐ NHANES/Predicted Exposure 
- ☒ Data Sources 
- ☐ Include ToxVal Data Availability 
- ☐ Assay Hit Count 
- ☐ Number of PubMed Articles 
- ☐ PubChem Data Sources 

 United States Environmental Protection Agency

HomeAdvanced SearchBatch SearchLists ▼PredictionsDownloads

Share

[DSSTox MS Ready Mapping File](#) Posted: 11/14/2016

The CompTox Chemistry Dashboard can be used by mass spectrometrists for the purpose of structure identification. A normal formula search would search the exact formula associated with any chemical, whether it include solvents of hydration, salts or multiple components. However, mass spectrometry detects ionized chemical structures and molecular formulae searches should be based on desalted, and desolvated structures with stereochemistry removed. We refer to these as "MS ready structures" and the MS-ready mappings are delivered as Excel Spreadsheets containing the Preferred Name, CAS-RN, DTXSID, Formula, Formula of the MS-ready structure and associated masses, SMILES and InChI Strings/Keys.

List Acronym	List Name	Last Updated	Number of Chemicals	List Description
FENTANYLS	LIST: Fentanyl Analogues	2021-04-22	67	A list of fentanyl analogues include both compounds developed by pharmaceutical companies and as designer drugs.